IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOGEN INTERNATIONAL GMBH and BIOGEN MA INC.,	)	
Plaintiffs,	)	**C.A. No. 17-823-LPS (Consolidated)**
v.	)	
AMNEAL PHARMACEUTICALS LLC, et. al,	)	
Defendants.	)	

BIOGEN'S PROPOSED FINDINGS OF FACT ON SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS AND INJUNCTIVE RELIEF

Of Counsel:

James B. Monroe
Eric J. Fues
Laura P. Masurovsky
Sanya Sukduang
Paul W. Browning
Li Feng
Andrew E. Renison
John E. Nappi
Jeanette M. Roorda
Aaron G. Clay
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Ave., N.W.
Washington, D.C. 20001
(202) 408-4000

Megan L. Meyers
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
271 17th Street NW, Suite 1400
Atlanta, GA 30363
(404) 653-6565

ASHBY & GEDDES
Steven J. Balick (#2114)
Andrew C. Mayo (#5207)
500 Delaware Avenue, 8th Floor
P.O. Box 1150
Wilmington, Delaware 19899
(302) 654-1888
sbalick@ashbygeddes.com
amayo@ashbygeddes.com

Attorneys for Plaintiffs

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Table of Abbreviations

MS	Multiple sclerosis
RRMS	Relapsing-remitting MS
DMT	Disease-modifying therapy
’514 patent	U.S. Patent No. 8,399,514
DMF	Dimethyl fumarate
MMF	Monomethyl fumarate
QD	Once daily
BID	Twice daily
TID	Thrice daily
MRI	Magnetic resonance imaging
ARR	Annualized relapse rate
EMA	European Medicines Agency
ANDA	Abbreviated New Drug Application
PTO	United States Patent & Trademark Office
Gd+	Gadolinium-enhancing
EDSS	Expanded Disability Status Scale
ECTRIMS	European Committee For Treatment and Research in Multiple Sclerosis
AAN	American Academy of Neurology
PTX	Plaintiffs’ Trial Exhibit
DTX	Defendants’ Trial Exhibit
PDX	Plaintiffs’ Demonstrative

I. INTRODUCTION

1. This matter was tried before the Court on December 6 and 9 and December 11 through 13, 2019. Being duly advised the Court now issues its findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

2. Plaintiffs Biogen International GmbH and Biogen MA Inc. ("Biogen" or "Plaintiffs") have no burden to prove in this case. Defendants have stipulated to infringement of the asserted claims of U.S. Patent No. 8,399,514 ("the '514 patent"). Defendants asserted invalidity based on obviousness, anticipation, lack of written description, lack of enablement, derivation, and improper inventorship. Defendants have not met their burden.

II. NATURE OF THE CASE

A. Parties

3. Information on the parties and experts who testified at trial is found in the Pretrial Order Ex. 1 (D.I. 347-1 at 2-12), Ex. 6 (D.I. 347-1 at 468-72), and Ex. 7 (D.I. 347-1 at 473-78).

B. Patent-in-Suit and Asserted Claims

4. Biogen MA Inc. f/k/a Biogen Idec MA Inc. is the owner of the '514 patent, entitled "Treatment for Multiple Sclerosis," issued on March 19, 2013. (DTX001 at 1.)

5. The '514 patent was filed on February 13, 2012 as U.S. Patent Application No. 13/372,426 ("the '426 application"). The '426 application is a continuation of U.S. Patent Application No. 12/526,296, filed as PCT/US2008/001602 on February 7, 2008. This PCT application claims priority to U.S. Provisional Application No. 60/888,921, filed on February 8, 2007. Pretrial Order Ex. 1 (D.I. 347-1 at Uncontested Fact No. 19.)

6. Biogen asserted that Defendants infringe claims 1-4, 6, 8-13 and 15-16 of the '514 patent ("asserted claims"). Pretrial Order Ex. 1 (D.I. 347-1 at Uncontested Fact No. 22.)

7. While each claim of the ’514 patent is separately presumed valid, 35 U.S.C. § 282, Claim 15 is illustrative:

> 15. A method of treating a subject in need of treatment for multiple sclerosis comprising orally administering to the subject pharmaceutical composition consisting essentially of (a) a therapeutically effective amount of dimethyl fumarate and (b) one or more pharmaceutically acceptable excipients, wherein the therapeutically effective amount of dimethyl fumarate is about 480 mg per day.

C. Tecfidera®

8. Tecfidera® is an oral medication indicated for treating relapsing forms of MS, administered twice a day, as capsules containing 120 mg of DMF for a starting dose of 240 mg a day, and as capsules containing 240 mg of DMF, for a total daily maintenance dose of 480 mg of DMF. (PDX003-20; Duddy 389:15-390:10.)

9. Tecfidera® is a disease-modifying therapy for MS. (Duddy 388:21-389:1, 17-20.)

D. Infringement

10. Defendants Hetero, MSN, Sandoz, Prinston and Shilpa have all stipulated that the commercial manufacture, use, sale, offer to sell and/or importation of their respective ANDA products prior to the expiration of the ’514 patent in accordance with the labeling proposed in their respective ANDAs would infringe the asserted claims pursuant to 35 U.S.C. § 271, provided those claims are not proven invalid or unenforceable. Zydus has stipulated that the submission of its ANDA constitutes infringement of the asserted claims of the ’514 patent pursuant to 35 U.S.C. § 271, provided those claims are not proven invalid or unenforceable.

III. THE ASSERTED CLAIMS OF THE '514 PATENT WERE NOT OBVIOUS

A. Unexpected Results

1. The Results for 480 mg/day Were Unexpected

a. 480 mg/day Demonstrated Unexpected Statistically Significant Efficacy

11. One skilled in the art would not have expected, and could not have predicted, the Phase III results based on the Phase II results. Biogen's Phase II study showed that 120 mg/day and 360 mg/day DMF were ineffective—only 720 mg/day showed any statistically significant efficacy. (DTX329 at 12-15; PDX003-21, 22; Duddy 391:13-392:8, 392:17-23; 393:3-9.)

12. In 2004, Biogen initiated its Phase II (six-month, placebo-controlled) clinical trial of BG-12 (DMF) in ten countries and enrolled 257 patients with RRMS. (PTX100 at BiogenF00006928; DTX329 at 1.) The study also included a six-month safety extension period. (PTX100 at BiogenF00006928; DTX329 at 8.) Ninety-one percent of the patients completed the placebo-controlled portion of the clinical trial. (PTX100 at BiogenF00006928.)

13. Patients were randomly assigned to one of four treatment groups for 24 weeks: (a) 120 mg DMF QD (120 mg/day); (b) 120 mg DMF TID (360 mg/day); (c) 240 mg DMF TID (720 mg/day); and (d) placebo. (PTX100 at BiogenF00006929; DTX329 at 8-9.)

14. The primary endpoint of the study was the sum of all new Gd+ lesions from four brain MRI scans obtained at weeks 12, 16, 20 and 24. (PTX100 at BiogenF00006929; DTX329 at 7.) Secondary endpoints included the cumulative number of new Gd+ lesions on scans from week 4 to week 24, the number of new or newly enlarging T2-hyperintense lesions at week 24, the number of new T1-hypointense lesions at week 24 and annualized relapse rate (ARR). (PTX100 at BiogenF00006929; DTX329 at 7.) Additional endpoints included disability progression as measured by Expanded Disability Status Scale (EDSS). (PTX100 at BiogenF00006929.)

15. Certain results of Biogen's Phase II study were reported in 2006. (DTX329 at 1; PTX100 at BiogenF00006929-30, BiogenF00006967-68; Duddy 390:13-18, 390:24-391:1.) The Phase II results showed that 120 mg/day and 360 mg/day did not exhibit a statistically significant difference compared to placebo for any of the primary or secondary endpoints. (DTX329 at 12-15; PTX100 at BiogenF00006930-33; Duddy 391:13-392:8.)

16. Contrary to Dr. Stobbe's testimony, the results for 360 mg/day did not suggest or indicate a trend toward efficacy. (Duddy 392:12-23.) For example, the results for 120 mg/day and 360 mg/day DMF in reducing new/newly enlarging T2 lesions were nearly identical to those for placebo. (DTX329 at 14.)

17. In contrast, the 720 mg/day DMF dose showed a statistically significant effect compared to placebo on the primary endpoint and all secondary endpoints except ARR. (DTX329 at 12-16, 20; PTX100 at BiogenF00006930-34; PDX003-21, 22; Duddy 391:13-392:8; 392:24-393:22; 400:8-20.) For example, patients administered 720 mg/day DMF showed a 69% decrease ($P<0.001$) in the mean number of new Gd+ lesions over MRI scans weeks 12 to 24 compared to placebo. (DTX329 at 12; PTX100 at BiogenF00006930.) Patients administered 720 mg/day DMF also showed a 48% decrease ($P<0.001$) in the mean number of new/newly enlarging T2-hyperintense lesions at week 24 compared to placebo. (DTX329 at 14; PTX100 at BiogenF00006932.) The reported Phase II results stated that BG12 (DMF) had a "32% reduction (240 mg tid vs placebo)" in ARR. (DTX329 at 20; PDX003-22.)

18. In Biogen's Phase III DEFINE trial, the results of which were published in 2012, the primary endpoint was the proportion of patients who had a relapse by two years. (DTX447 at 1; PDX003-24; Duddy 403:10-12; 404:15-17.) Other endpoints included ARR, the number of new

and enlarging T2-weighted lesions, the number of Gd+ lesions and confirmed progression of disability. (DTX447 at 1; PDX003-24; Duddy 404:15-21.)

19. 1237 patients in DEFINE were randomly assigned to one of three treatment groups: (1) 240 mg DMF BID (480 mg/day), (2) 240 mg DMF TID (720 mg/day), and (3) placebo. (DTX447 at 1, 4; PDX003-24; Duddy 404:22-23.) For each of the endpoints, the results for 480 mg/day and 720 mg/day DMF were statistically significantly better than those for placebo. (DTX447 at 1; PTX100 at BiogenF00006935-36.) Moreover, the results for the 480 mg daily dose were similar to those with the 720 mg daily dose for each end point measured. (DTX447 at 1; PDX003-27; Duddy 406:9-407:10.)

20. The estimated proportion of patients who had a relapse by two years was significantly lower in groups dosed with 480 mg/day and 720 mg/day than in the placebo group (27% with 480 mg/day and 26% with 720 mg/day vs. 46% with placebo, $P<0.001$ for both comparisons). (DTX447 at 1; PDX003-27; Duddy 406:9-407:10.) Clinicians find this primary endpoint particularly useful, because it "look[s] at each individual's unique chance of getting through the two years, whether they relapse once or many times or not at all." (Duddy 406:12-19.) Thus, if 100 patients are dosed with 480 mg/day DMF, approximately "20 people will be relapse free at the end of that two years, who would have relapsed if they had been on placebo." (*Id.* 407:2-10.)

21. "[T]he 480 [mg/day] dose reduced [relapse rate] by 53 percent, [and] 720 [mg/day] by 48 percent, so hovering on either side of 50 percent." (Duddy 405:24-25.) Specifically, the annualized relapse rate at 2 years was 0.17 for patients dosed with 480 mg/day and 0.19 for those dosed with 720 mg/day, as compared to 0.36 for the placebo group, representing relative reductions

of 53% and 48% for the 480 mg/day and 720 mg/day doses, respectively (P<0.001 for both comparisons). (DTX447 at 1.)

22. The estimated proportion of patients in DEFINE with confirmed progression of disability was 16% for those dosed 480 mg/day, 18% for those dosed 720 mg/day and 27% for those dosed with placebo, with significant relative risk reductions of 38% for 480 mg/day (P=0.005) and 34% for 720 mg/day (P=0.01). (DTX447 at 1.)

23. In Biogen's Phase III CONFIRM trial, the results of which were published in 2012, the primary endpoint was ARR over two years. (DTX446 at 1; Duddy 403:18-19.) Other endpoints included the proportion of patients who had a relapse by two years, the number of Gd+ lesions, the number of new and enlarging T2-hyperintense lesions, the number of new T1-hypointense lesions and progression of disability. (DTX446 at 1; PDX003-25.)

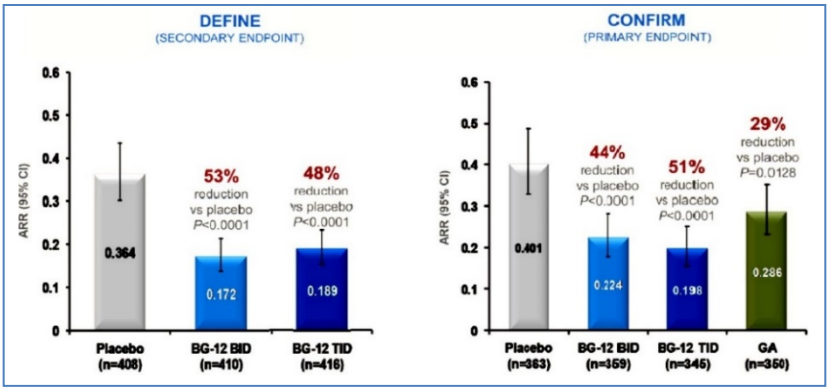
24. 1430 patients in CONFIRM were randomly assigned to one of four treatment groups: (1) 240 mg DMF BID (480 mg/day), (2) 240 mg DMF TID (720 mg/day), (3) subcutaneous daily injections of 20 mg glatiramer acetate for 96 weeks, and (4) placebo. (DTX446 at 1, 3; PDX003-25; Duddy 405:1-13.) For each of the endpoints except progression of disability, the results for 480 mg/day were statistically significantly better than those with placebo. (DTX446 at 1.)

25. At two years, 480 mg/day and 720 mg/day reduced the relapse rate by approximately "50 percent, 480 [mg/day] at 44 percent reduction, [720 mg/day] at 51 percent reduction." (Duddy 406:1-3.) Specifically, the ARR was significantly lower with 480 mg/day DMF (0.22), 720 mg/day DMF (0.20) and glatiramer acetate (0.29) than with placebo (0.40) (relative reductions: 480 mg/day DMF, 44% (P<0.001); 720 mg/day DMF, 51% (P<0.001); glatiramer acetate, 29% (P=0.01) (DTX446 at 1.) As compared to placebo, 480 mg/day DMF,

720 mg/day DMF and glatiramer acetate significantly reduced the numbers of new or enlarging T2-weighted hyperintense lesions (all P<0.001) and new T1-weighted hypointense lesions (P<0.001, P<0.001 and P=0.002, respectively). (*Id.*)

26. During prosecution of the '514 patent application, Richard A. Rudick, M.D. submitted a July 30, 2012, declaration, detailing the unexpected results from Biogen's DEFINE and CONFIRM studies. (DTX017 at 1; Duddy 403:20-404:3; 405:17-406:8.) The DEFINE and CONFIRM results are summarized in Figures 3-5 in Dr. Rudick's declaration. (DTX017 at 7-8.)

27. For example, Figure 3 in Dr. Rudick's declaration showed the surprising efficacy of the 480 mg daily dose in statistically significantly reducing ARR compared to placebo:



(DTX017 at 7; PDX003-26.) The reduction in ARR seen in both Phase III trials also demonstrates that 480 mg/day has similar efficacy in treating MS to 720 mg/day. (Duddy 405:14-406:8.)

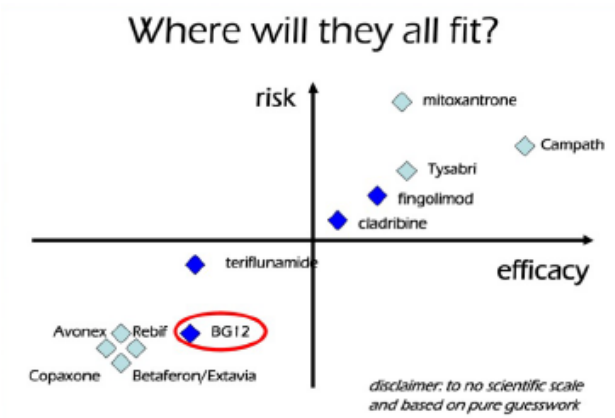
b. 480 mg/day Demonstrated an Unexpected Magnitude of Effect

28. One skilled in the art would not have expected that 480 mg/day would be effective in treating MS, let alone similarly efficacious to 720 mg/day, based on Phase II. As Dr. Duddy testified, "absolute surprise that we have a drug at a dose not tested, not only doing better than the new expectations that we had, but actually overtaking the higher dose, and then landing in very much the same efficacy range as that higher dose after the phase III." (Duddy 402:20-403:2; *see also id.* 488:17-20.)

29. The magnitude of the effect—clinical and radiological—seen in Phase III was not anticipated by the MS community. In 2007, injectable MS therapies interferons and glatiramer acetate reduced relapse rate by 30%—Dr. Lindsey characterized these therapies as "modestly effective." (Lindsey 121:18-122:5; 152:13-153:6; *see also* Duddy 389:6-7 ("So we have first line low efficacy injectable therapies."; DTX329 at 2 ("Significant unmet need for multiple sclerosis (MS) therapies. ~30% relapse reduction by current disease-modifying therapies.").

30. Similarly, 720 mg/day demonstrated an "unimpressive, interferon like" relapse rate reduction of roughly 30% in Phase II. (Duddy 487:8-11; DTX329 at 16, 20; PDX003-22.)

31. In a 2009 presentation to MS nursing professionals before the Phase III results were known, Dr. Duddy anticipated that the 720 mg/day dose of DMF (BG12) from Phase II would occupy the same therapeutic space—low efficacy, low risk—as the interferons in treating MS:

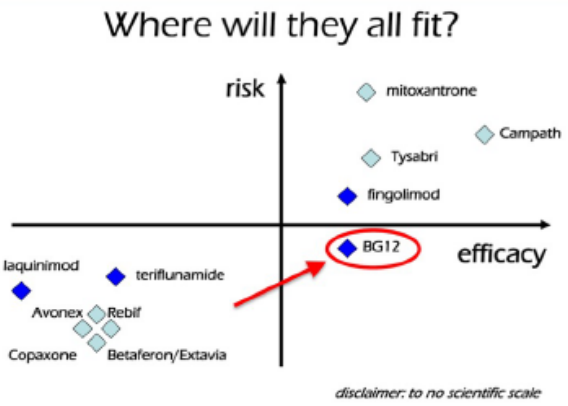


(DTX495 at 30; PDX003-23, 28.) Based on Phase II, Dr. Duddy expected that DMF (BG12) dosed at 720 mg/day would reduce the ARR by roughly 30%, similar to interferons and glatiramer acetate. (Duddy 389:5-7; 393:14-395:22; 398:8-13, 398:17-23; 400:21-401:7; 430:13-15.)

32. Discussing his 2009 presentation, Dr. Duddy explained that "the general tendency in MS drugs [is] these tend to lie on a diagonal, which you see, which is that drugs tend t[o] be either relatively risk free and well tolerated but not all that efficacious, which puts them down in

the bottom left quadrant, or they tend to be in the top right quadrant where we have a higher level [of] efficacy, but you have to sacrifice tolerability and risk with that." (Duddy 395:6-15.) Dr. Duddy explained that the "best quadrant is the one of the two that is sadly empty here, which is one to look at a drug that is high efficacy and low burden of drug, so the bottom right quadrant." (*Id.* 396:1-4.) As for DMF, Dr. Duddy testified that the "data we have seen with roughly that estimated 30 percent reduction and a safety profile which was described as the drug being generally safe and well tolerated, I felt that it belonged on the phase II data and would therefore be predicted to be close to the interferons, which is where I put it." (*Id.* 395:17-22.)

33. Dr. Duddy's November 2011 presentation after the Phase III results were announced illustrated the extent to which the Phase III results greatly changed the MS community's perception of the drug. In his 2011 presentation, Dr. Duddy reappraised the drug's efficacy, while maintaining its favorable safety profile:



(PTX403 at 45; PDX003-28.) Dr. Duddy expressed his surprise at the high level of relapse rate reduction and strength of the MRI results by both the 480 mg/day and 720 mg/day, given the modest magnitude of efficacy of 720 mg/day seen in Phase II. (Duddy 402:5-403:2; 408:3-409:3.)

34. Moreover, contrary to the tendency for MS therapies to sacrifice safety for greater efficacy, DMF at 480 mg/day achieved an unexpected balance of favorable safety profile and high

efficacy. (*Id.* 401:8-25; 408:15-25 ("[Tecfidera] has now moved significantly to the right. So again, with that roughly 50 percent I put it in line with another drug of 50 percent, which moves into a higher efficacy. Again, I was impressed that there had been really nothing here that changed my view on the drug safety or tolerability. When we see the phase III results, so it remains in the same quadrant in the same half of that, putting it in a quadrant of a drug with higher efficacy, but with lower risk of tolerability issues.").

35. Consistent with Dr. Duddy's opinions, Defendants' expert Dr. Lindsey also found Biogen's Phase III results unexpected and surprising based on the Phase II results. On his personal website educating the public about MS (PTX213 (stating that one purpose is to "serve as an information resource" and "the opinions here are my own"); PDX003-23; Lindsey 153:7-20), he reported Biogen's Phase II results, presented at the September 2009 ECTRIMS meeting, stating that BG12 (DMF) "reduced relapse rate by about 30% compared to placebo" (PTX214) similar to interferons and glatiramer acetate MS therapies. (Lindsey 121:18-122:1; 153:2-6; 154:21-155:3; Duddy 399:3-25.) Like Dr. Duddy's opinions at the time, Dr. Lindsey added that "[t]he combination of increased effectiveness and safety is elusive." (PTX214; Lindsey 155:4-21.)

36. Dr. Lindsey expressed his surprise at the impressive and unexpected results of Biogen's Phase III DEFINE study. From the ECTRIMS 2011 meeting, Dr. Lindsey stated that the "most important results were from a Phase III study of a drug called BG12." (PTX215; PDX003-31; Lindsey 156:5-18.) Dr. Lindsey, commenting on dosing "either 2 or 3 times a day," noted the "annual relapse rate on placebo was 0.364, while it was 0.172 on the lower dose BG12 and 0.189 on the higher dose of BG12. This is a reduction of 53 or 48% in the relapse rate." (PTX215; *see also* Lindsey 156:19-22.) Dr. Lindsey also noted that to the 480 mg/day dose, "[t]here was also a marked effect on MRI activity, with a reduction of about 90% in enhancing lesions and 85% in

new T2 lesions." (PTX215.) Dr. Lindsey therefore reported that "[t]hese are ***impressive results, both for efficacy and safety.*** In their Phase II study (see the report from ECTRIMS 2009) this drug reduced relapse rate by 30%, so these results are a little ***surprising***." (*Id.*) (emphasis added).

37. Consistent with Dr. Duddy's testimony, Dr. Lindsey testified as to the first Phase III study that "there was a . . . considerably better effect in the phase III studies . . . . So [the Phase III results] were ***better than I would have expected***." (Lindsey 157:14-21; Duddy 411:20-412:17; *see also* Lindsey 156:23-158:5 (Q: Aside just from the posting, you believed that these results were a lot better in phase III than the phase II results would have led you to expect; is that right? A: Yes, I was expecting about a 30 percent reduction in relapse rate from phase III based on what we had found in phase II.")) (emphasis added). Dr. Lindsey concluded that a "second phase III study is in progress, and the results should be available soon. If they see the same benefits, this will be an attractive medicine." (PTX215.)

38. After hearing Biogen's Phase III CONFIRM results reported at the AAN 2012 meeting, Dr. Lindsey similarly praised its positive results. He commented on the tested DMF doses, *i.e.*, 480 mg/day and 720 mg/day, and their respective reductions in relapse rate compared to placebo—44% and 51%. (PTX216; PDX003-31.) He also reiterated that "[t]he results of the first Phase III study (see ECTRIMS 2011) were ***quite impressive***." (PTX216 (emphasis added); Lindsey 158:10-25; Duddy 414:12-14.)

39. Dr. Lindsey's analysis and testimony confirms that skilled artisans can compare results at different doses in the same clinical trial and across clinical trials. (Lindsey 163:13-14.)

40. The radiological outcomes in Phase III also surprised skilled artisans. In Phase II, 720 mg/day statistically significantly reduced new/newly enlarging T2 lesions by 48%. (DTX329 at 14; PDX003-22; Duddy 393:5-9, 400:15-16.) Dr. Duddy testified that T2 lesion reduction is

"an important one for clinicians" and "helps us form a view of the magnitude of the effect we're likely to see clinically." (Duddy 393:5-9.) Contemporaneous with the Phase II results, other MS therapies showed "T2 reduction rates of 80 percent. 50 percent is well short of what we have been seeing with therapies whose level of magnitude that we already know." (Duddy 393:10-14.) In the DEFINE Phase III study, 720 mg/day unexpectedly reduced T2 lesions by 74%, and 480 mg/day exceeded this effect with an 85% reduction. (Duddy 402:8-403:2; DTX447 at 6-7.) One skilled in the art would therefore not have predicted the magnitude of effect of 720 mg/day in a longer, bigger study, nor that a lower dose of 480 mg/day would exceed that effect.

2. The Phase III Results Surprised Biogen Personnel and Investigators

41. The reactions of Biogen personnel and investigators involved in developing Tecfidera® when they first analyzed and announced the Phase III results further evidences the surprising and unexpected nature of those results.

42. Dr. Dawson, who led the Phase III studies and carried Tecfidera® through FDA approval (Dawson 284:15-23; 285:6-11), and others involved in the clinical studies expected 720 mg/day DMF in the Phase III trials to reduce ARR by approximately 30% based on the Phase II results. (Dawson 318:15-319:14; 334:3-4; 335:21-23; 340:22-341:12; PTX114 at BiogenF10157883.)

43. Dr. Dawson testified that when Biogen statisticians unblinded and calculated the clinical data, "they were so surprised with the results that actually ***they figured they did something wrong*** and they started over from the beginning and completely reanalyzed the study." (Dawson 333:9-17; *see also id.* 333:18-334:14) (emphasis added). Before Dr. Dawson disclosed the DEFINE results to the principal investigators—esteemed clinicians in the field—they predicted relapse rate reductions for 720 mg/day from "high 20s" to "high 30s." (*Id.* 338:17-25; 341:2-12.) When informed of the results for 720 mg/day, "[t]hey were incredibly thrilled and excited. It was

very unexpected." (*Id.* 341:13-14.) Dr. Dawson also testified that when they were similarly asked about the 480 mg/day dose, "the thinking was that it would be less efficacious than the 720 milligram dose, and when we told them that the actual effect . . . was 53 percent effect on relapses, they were again, very surprised." (*Id.* 341:17-23; *see also id.* 342:1-3.)

44. Dr. Dawson was similarly surprised and amazed at the results. (Dawson 333:9-334:14.) During prosecution of the '514 patent application, Dr. Dawson submitted a declaration detailing the unexpected results of the Phase III DEFINE trial. (Dawson 303:20-24; PTX100.) Consistent with her trial testimony, Dr. Dawson explained in her declaration that one skilled in the art would not have a reasonable expectation that 480 mg/day DMF would provide statistically significant and clinically meaningful effectiveness for treating MS, and one skilled in the art would have been very surprised that 480 mg/day was similarly efficacious to 720 mg/day. (PTX100 at BiogenF00006945-46) ("Even more unexpected . . . was the magnitude of treatment effect of the DEFINE study -- the 480 mg/day dose demonstrated similar efficacy to the 720 mg/day dose on both clinical and MRI measures of MS disease activity -- with a *high level of statistical significance*.") (emphasis in original).

3. The Phase III Results Amounted to A Difference in Kind

45. The difference in results between Biogen's Phase II and Phase III clinical trials amounts to a difference in kind. Based on the Phase II results, skilled artisans expected DMF dosed at 720 mg/day to exhibit, at best, interferon-like efficacy. *See supra* Section III.A.1. And skilled artisans would not have expected that a lower 480 mg/day dose would treat MS with any meaningful efficacy, let alone on the same scale as 720 mg/day. *See supra* Section III.A.1-2.

46. The Phase III results, however, showed not only that 480 mg/day and 720 mg/day greatly exceeded efficacy expectations based on the Phase II 720 mg/day results, but also that the

lower 480 mg/day dose demonstrated an unexpected magnitude of effect similar to 720 mg/day in Phase III, and even exceeded it in some respects. (Duddy 402:5-403:2; 488:4-23.)

47. MS Trust, a group providing information to MS patients and educating MS health professionals, classifies Tecfidera® as a more effective MS treatment than interferons, elevating it to a higher class of MS therapies distinct from the less effective interferons. (PTX429; PDX003-30; Duddy 409:9-411:6; 413:3-11.)

B. Additional Objective Indicia of Nonobviousness

1. Long-Felt But Unmet Need

48. As of 2007, no oral medications had been approved to treat MS. (PDX003-19; PDX004-10; Duddy 389:2-14.)

49. MS is a chronic autoimmune disease requiring lifelong therapy. (Lindsey 130:13-17) ("[I]t's a chronic disease, it's life long and once you have it, you continue to get new symptoms over the rest of your life. And so if you're thinking specifically about treating MS, it's going to be a chronic, life-long treatment.").

50. Injectable and infusion MS therapies were available in 2007, but they required regular injections or monthly parenteral infusions and had significant limitations. (Lindsey 155:15-17 ("[B]oth of the available treatments that we were using, the interferon and the [glatiramer] are given by injections which people generally don't like."); Duddy 389:5-14.)

51. For many patients, these medications were often associated with injection anxiety or injection-related adverse effects, limiting long-term adherence to treatment and leading many patients to decline disease-modifying therapy entirely. (Duddy 415:1-416:2; 417:8-14.)

52. After the '514 patent filing date, two oral medications received FDA approval. In 2010, the FDA approved Gilenya® (fingolimod) capsules to treat patients with relapsing forms of MS. Fingolimod, however, did not satisfy the need for an oral MS medication due to safety

concerns including teratogenicity, a potentially serious problem for women 20-45 years old, the most common group treated for MS (Duddy 418:21-419:3), high blood pressure and cardiotoxicity (*Id.* 418:17-19; PTX403 at 40) and liver toxicity. (Duddy 418:616-17; PTX403 at 40; PDX003-32.) These safety concerns led the EMA, for example, to approve fingolimod as a second-line treatment. (Duddy 418:6-16.)

53. Aubagio® (teriflunomide), available in 2012, similarly failed to meet the need for an oral MS therapy due to its safety concerns, including potential birth defects, liver toxicity and hair loss, and required fortnightly blood tests (necessitating venipuncture). (Duddy 419:6-420:5; PDX003-33.) Accordingly, while a relatively small segment of MS patients began therapy with these drugs, they did not meet the long-felt need for an oral MS therapy. (Duddy 420:3-5; 420:10-15.)

54. Biogen never received FDA approval of 720 mg/day DMF to treat MS (Stobbe 249:18-21).

55. Tecfidera®, the commercial embodiment of the claimed invention (Duddy 389:15-20), satisfied the long-felt, unmet need for a safe, effective, first-line oral MS therapy. As an oral medication, it brought significant twice-daily convenience to patients and greatly enhanced compliance, balancing therapeutic efficacy with tolerability, thus improving long-term benefits compared to injectable MS therapies. (Duddy 413:22-417:1; 417:8-18; 421:12-23.) In Dr. Duddy's practice, "Tecfidera was really very disruptive," leading to surprise not only at "the number of people who were injecting who switched," but at "the amount of unexpressed need" by his patients. (Duddy 414:22-416:14; 421:12-23.)

2. Commercial Success

a. Tecfidera®'s Marketplace Success

56. The marketplace success of Tecfidera® is not disputed. Since its March 2013 launch, Tecfidera® has achieved blockbuster status through 2018, including 2013, on an annualized basis, with total U.S. sales of $15.9 billion. (Jarosz 736:3-739:23; PDX006-6; PTX732 at Tab 20; PTX494 at BiogenF600006591, 6641.) Relative to other disease-modifying MS therapies, Tecfidera® has enjoyed more success. The market for MS DMTs falls "generally into three classes--oral therapies, self-injected therapies, and intravenous or infused therapies. Within those classes, there are quite a number of options available to the marketplace. And at the end of 2018, there were at least 15 different solutions across those three classes . . . . It's a very crowded field, in part because it's a very serious disease . . . ." (Jarosz 727:19-728:6.) By any comparison, Tecfidera® "has performed very well." (*Id.* 728:7-8.)

57. Compared to other blockbuster MS DMTs in 2018, Tecfidera® led all products "on a revenue basis" and "comprised about 20 percent . . . of the marketplace of these 15 or 18 different competitors . . . ." (Jarosz 740:9-741:21; PDX006-7; PTX732 at Tab 8.)

58. Compared to Gilenya® and Aubagio®, Tecfidera® had nearly doubled their market share by 2018 despite its later marketplace introduction. (Jarosz 742:1-743:15; PDX006-8; PTX732 at Tab 18.) Indeed, Tecfidera® "became the country's number one prescribed oral therapy for relapsing forms of MS after six months." (Jarosz 728:18-25; PTX062 at BiogenF70000520.)

59. Tecfidera has been and remains a tremendous marketplace success. (Jarosz 745:6-9 ("The drug has been very successful and continues to be successful. It entered a very crowded marketplace. It obtained immediate success and it has sustained that success.").)

60. Contrary to industry norms, Tecfidera® performed "well in excess of what was projected" by Biogen. (Jarosz 745:14-746:6 ("Typically, actual performance is less than projected

performance . . . . In this case, however, the actual performance of Tecfidera was well in excess of what was projected."); PDX006-9; PTX732 at Tab 21.)

61. Tecfidera® also received significant praise and recognition shortly after launch and one year later. (Jarosz 746:11-747:16; PTX063 at BiogenF10159765; PTX064 at BiogenF10159754; PTX651 at BiogenF70016309-10; PTX547 at BiogenF10159757.

62. Defendants' expert, Mr. Hofmann, does not dispute Tecfidera®'s success, sales figures or its blockbuster status. (Hofmann 790:6-9 ("I think the data sets and whatnot do reflect the marketplace performance of Tecfidera."); 820:11-24.) Mr. Hofmann agreed that by Q4 2018, Tecfidera® had more sales than any other product to treat MS in the country. (Hofmann 821:15-822:4; 822:15-823:7; PDX007-1.) In sum, Mr. Hofmann testified, "the numbers tell a pretty positive story." (Hofmann 823:13.)

63. Mr. Hofmann had no reason to believe that discounts and allowances for Tecfidera® differed from those for the other oral DMTs, Gilenya® and Aubagio®. (*Id.* 821:1-14.)

64. Biogen's and ANDA filers' investments and business planning further demonstrates Tecfidera®'s success. Biogen has invested significant resources in developing Tecfidera®. (Jarosz 729:24-733:1; PDX006-5; PTX494 at BiogenF600006667.)

65. Defendants have committed substantial resources pursuing market entry through regulatory approval and litigation. (Jarosz 733:2-736:2.)

66. One ANDA filer's failed attempt to file on the first possible regulatory date prompted a lawsuit where it alleged to have lost "tens if not hundreds of millions of dollars in revenue it otherwise would have earned through the sale of its generic version of Tecfidera®." (*Id.* 733:20-734:15, 735:4-10; PTX211 at 17-18.)

67. Mr. Hofmann admitted that claims in a published patent application can change before issuance of a patent. (Hofmann 810:9-12; DTX321.)

68. Mr. Hofmann agreed that U.S. Patent No. 7,320,999 (DTX341) issued after the '514 patent's 2007 filing date. (Hofmann 810:4-8.)

69. Mr. Hofmann did "not offer[] technical opinions" nor rely on any as to whether others could not develop DMF formulations outside the scope of the claims of U.S. Patent No. 6,509,376. (Hofmann 819:4-23; DTX340.)

b. Causal Nexus

70. Tecfidera®'s success, in large part, has been driven by the benefits of the claimed invention for a treatment of MS, namely, efficacy, safety, tolerability and convenience. Mr. Jarosz testified as to the benefits of the patented invention. "[T]he invention allows for a unique combination of four elements—efficacy, tolerability, safety and convenience. That unique combination is achieved because of the dosing of 480 milligrams, which comes in two doses a day . . . . I understand that dosing yielded unexpected efficacy with improved patient compliance." (Jarosz 748:11-18; *see also id.* 771:2-4; PDX006-12.)

71. Mr. Jarosz further explained that, in addition to evidence of the clinical importance of the patented benefits, Drs. Duddy's and Wynn's technical opinions and testimony provided a basis for his understanding of the patented invention's benefits as a driver of Tecfidera®'s marketplace success. Specifically, Mr. Jarosz relied on a conversation with Dr. Wynn, Dr. Wynn's expert reports and Dr. Duddy's trial testimony about the patented invention's benefits. (Jarosz 748:21-24; 749:3-4; 771:10-16; 772:15-20.)

72. Mr. Hofmann does not dispute the importance of the patented invention's attributes: "I think it is true that efficacy, safety, tolerability and convenience are important drivers of the sales of Tecfidera . . . ." (Hofmann 802:13-15; *see also id.* 804:15-18 ("[S]afety, efficacy,

tolerability, convenience are things that are important to the commercial performance of Tecfidera . . . .").)

73. Biogen materials providing guidance on marketing messages highlight the patented invention's attributes, namely efficacy, safety, tolerability and convenience. (Jarosz 749:8-750:4; PDX006-13; PTX089 at BiogenF10166092, BiogenF10166097.) Additional marketing materials, including website-accessed information intended for physicians and patients, further highlight the patented invention's attributes of efficacy, safety, tolerability and convenience. (Jarosz 750:7-751:8, 756:7-11; PDX006-14; PTX457; PTX459; PTX460; PTX461.)

74. The New York Times and Investor's Business Daily articles highlight the aforementioned benefits of efficacy, safety and tolerability. (Jarosz 751:12-752:1; PDX006-15; PTX651 at BiogenF70016309-10; PTX064 at BiogenF10159754; *see also* PTX063; PTX547.)

75. The Northstar Metric Tracker, which follows the "behaviors and preferences of neurologists," found that "no MS drug consistently was perceived by the neurologists to be better than Tecfidera in both efficacy and safety," specifically, "[t]here was no drug that was higher than Tecfidera on the combination of efficacy and safety." (Jarosz 752:5-22; PDX006-16.)

76. Mr. Jarosz testified that Biogen's marketing materials and third-party perceptions of the clinical importance of the patented invention indicate "[t]he advantages of the claimed invention matter in the marketplace. There is a causal nexus between the patented invention and the success of Tecfidera." (Jarosz 753:1-2.)

77. "Pricing and marketing and promotion" do not detract from the patented benefits as significant drivers of Tecfidera®'s commercial success. (*Id.* 753:4-19.) Pricing for Tecfidera® and oral DMTs Gilenya® and Aubagio® "track[] one another fairly closely." (*Id.* 753:21-754:13; PDX006-17; PTX732 at Tab 19.) Accordingly, "pricing alone is not responsible" for Tecfidera®'s

commercial success. (Jarosz 754:10-13; *see also id.* 754:14-756:11.) Rather, "Tecfidera has been a success in the marketplace and its success has in large part been due to the patented invention. As a result, the patent is a commercial success." (*Id.* 756:15-17.)

3. Copying

78. Over twenty-five ANDA filers, six of whom litigated at trial, are directly copying Tecfidera® and its use as claimed in the '514 patent. (Wynn 639:25-640:15; PTX174 at HETERO00032910; PTX176 at MSN_DMF 0000076; PTX177 at MSN_DMF 0041063; PTX178 at MSN_DMF 0043534; PTX182 at Sandoz_DMF 0000087; PTX183 at Sandoz_DMF 0000027; PTX184 at Sandoz_DMF 0019558; PTX190 at Prinston_DMF 0000431; PTX206 at SHILPA00020418; PTX207 at ZYDDMF0 016819.)

IV. BIOGEN IS ENTITLED TO INJUNCTIVE RELIEF

79. Defendants did not oppose Biogen's injunctive-relief evidence presented at trial. Mr. Jarosz provided unrebutted testimony about the irreparable harm to Biogen upon market entry of generic equivalents to Tecfidera® for which there is no adequate legal remedy (Jarosz 756:22-762:3; PTX518 at BiogenF600003877; PDX006-20), the balance of harms warranting entry of a permanent injunction (Jarosz 762:7-763:10; PDX006-21; PTX732 at Tab 24), and furtherance of the public interest in enjoining Defendants from market entry. (Jarosz 763:15-25.)

V. CONCLUSION

80. Defendants have stipulated to infringement of the asserted claims of the '514 patent.

81. Unexpected results and additional objective indicia of nonobviousness confirm the nonobviousness of the patented invention.

ASHBY & GEDDES

/s/ Steven J. Balick

Steven J. Balick (#2114)
Andrew C. Mayo (#5207)
500 Delaware Avenue, 8th Floor
P.O. Box 1150
Wilmington, Delaware 19899
(302) 654-1888
sbalick@ashbygeddes.com
amayo@ashbygeddes.com

Attorneys for Plaintiffs

Of Counsel:

James B. Monroe
Eric J. Fues
Laura P. Masurovsky
Sanya Sukduang
Paul W. Browning
Li Feng
Andrew E. Renison
John E. Nappi
Jeanette M. Roorda
Aaron G. Clay
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Ave., N.W.
Washington, D.C. 20001
(202) 408-4000

Megan L. Meyers
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
271 17th Street NW, Suite 1400
Atlanta, GA 30363
(404) 653-6565

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